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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) TSR-10002/38	
	Application Number 10/706,738-Conf. #7532	Filed November 12, 2003
	First Named Inventor John Hilfinger	
	Art Unit 1635	Examiner R. A. Schnizer

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant /inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 39,204

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

/Avery N. Goldstein, Ph.D./
Signature

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Typed or printed name

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November 19, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John Hilfinger	Attorney Docket No. TSR-10002/38
Serial No.:	10/706,738	Group Art Unit: 1635
Filing Date:	November 12, 2003	Examiner: Richard Schnizer
For:	METHODS AND COMPOSITIONS OF GENE DELIVERY AGENTS FOR SYSTEMIC AND LOCAL THERAPY	

PRE-APPEAL BRIEF REQUEST FOR REVIEW
STATEMENT OF ARGUMENTS

Mail Stop AF, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Dear Sir:

With a concurrent filing of the Notice of Appeal, Applicant requests review of the above-referenced application on the basis of the following remarks.

Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012). In addition, claims 15 and 16 stand rejected under 36 U.S.C § 103(a) as being unpatentable as to the base claim and in further view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002). Claims 11, 12, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable as to the base claim and in further view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Remarks Directed to the Rejection of Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski, in view of Keener and Gebeyehu:

These rejections are based on the assertion on that: "It would have been obvious to one of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski." (Paper No. 20070907, pg. 4). Further, that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide [of

Gebeyehu] for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in the art as equivalents. (Id. at 5.)

Argument 1: Niedzinski in view of Keener fails to render the A-R_1 moiety obvious in the instant inventive method.

Examiner bridges Niedzinski with Keener because "Niedzinski considered his conjugation technique to be applicable to a variety of bile acids (see last sentence of column 1 on page 724), and it was clear that it could be applied to either the C3 hydroxyl (sic), so the presence of a carboxyl group was not required." (Paper No. 20070907, pg. 3) (emphasis added).

As was recently articulated by the Federal Circuit, for a case of *prima facie* obviousness to be found for chemical matter, "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." Takeda Chem. Indus., Ltd. v. Alphapharm Pty, LTD, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007). The court further made expressly clear that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." Id. (quoting In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (internal references omitted). The court clarified that this test for chemical compounds is "consistent with the principles enunciated in KSR." Id. (citing KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007).

The rejections of independent claims 8 and 20 fail to satisfy a prima facie case of obviousness as enunciated in Takeda. It is flawed logic to allege that simply because other bile acids are amenable to modification by a sample synthetic strategy that the reference provides adequate support for using un-C(3)-functionalized bile acids as biologically functional agents for the instantly claimed use. Indeed, a person having ordinary skill in the art recognizes that Niedzinski is limited to teaching that both C(3)-functionalization and a C(24)-allyl group creates a molecule that when used in as an additive to other transfection agents enhances or inhibits delivery of conjugated DNA in digestive fluid- not that

Niedzinski's molecules are biologically functional equivalents to the un-C(3)-functionalized molecules used in the instantly claimed invention.

Examiner asserts that the above fact "is immaterial" and that "Applicant has presented no reason or evidence why one of ordinary skill would not expect the invention of Niedzinski to function with other C(3) bile acid conjugates, or for that matter with other bile acid conjugates corresponding to Niedzinski's C(24) conjugates." (Paper No. 20070907, pg. 10). The provocative assertion found in Paper No. 20070907 on page 9 that Niedzinski does not recite derivatization at the C(3) position is a gross mis-interpretion of the reference and steroid chemistry nomenclature. First, Niedzinski does not teach the activity of any C(24) conjugate in the absence of C(3)-functionalization: all Niedzinski disclosed compounds that are C(24) modified are **ALWAYS** also C(3) modified. Further, in Niedzinski the only modification to C(24) is alkyl esterification, and a teaching of relevance to DNA binding domains at C(24) is simply not present per the pending claims. Further, a proper analysis of the scope of the instant claims makes clear that the C(3) position is unmodified in all members of the claimed group. Thus, it is immaterial that C(3)-functionalized cholic acid may function similarly to other C(3)-functionalized bile acids because the instant invention does not claim any C(3)-functionalized bile acids. The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. In re Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999). A person skilled in the art readily recognizes that in order for A-R_1 to be any of the claimed group that modification of C(3) must be absent. The assertions of the Office notwithstanding that neither Neidzinski nor applicant did gastric fluid stability experiment without added lipid addition, such data is in fact found in the instant specification with respect to Figures 5-7.

As there is no teaching or suggestion in either the cited prior art or the cited knowledge in the art to use un-C(3)-functionalized bile acids to deliver nucleic acid to target cells, a prima facie case of obviousness under 35 U.S.C. §103 as defined by KSR and Takeda has not been met.

Argument 2: Niedzinski and Keener in view of Gebeyehu fails to render the A-R_1-Q-Z or A-R_1-Q-Y-Z moieties obvious in the instant inventive method.

The further teaching of Gebeyehu also fails to sustain a prima facie case of obviousness. Gebeyehu is referred to on page 11 of Paper No. 20070907:

> Regarding Gebeyehu, Applicant argues that the reference does not teach or suggest the use of any cholesterol derivative other than stigmasterol, ergosterol, or cholic acid. Gebeyehu was not relied upon to teach any derivative other than these. The cholesterol derivatives are taught by Niedzinski and Keener. Gebeyehu taught the use of nucleic acid binding domains, such as a polyamine or a polycationic peptide, in combination with a steroid such as cholic acid, stigmasterol, or ergosterol, and a linker. Clearly polyamines and cationic peptides were recognized in the art as equivalents as DNA binding domains in delivery compositions, such that it would have been obvious to substitute one for the other in the invention of Niedzinski as modified by Keener.

Thus, Gebeyehu is cited merely for the proposition that polyamines and cationic peptides are art recognized equivalents. (*see also* Paper No. 20070907, pg. 5.) The failure to make a prima facie case of obviousness based on Niedzinski in view of Keener is not corrected by any teaching or suggestion in Gebeyehu. In sum, Niedzinski in view of Keener in further view of Gebeyehu fails to establish a prima facie case of obviousness for all elements of the instantly claimed invention.

Remarks Directed to the Rejection of Claims 15, and 16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski in View of Keener and Gebeyehu in Further View of Perrie:

Applicant incorporates in its entity the above remarks regarding Niedzinski in view of Keener and Gebeyehu in that, alone or in combination, they are deficient in rendering obvious the claimed invention.

Perrie et al. is limited to teaching oral administration of a liposome entrapped plasmid DNA molecule. This route of administration is distinct from the subject claims. Perrie teaches that DNA by entrapment into liposomes is essential to its protection. (p. 186, Introduction; p, 190.) Niedzinski supports Perrie by teaching function of cholate amphiphiles when used as additives to liposomes. As such, the Perrie method of delivery contraindicates the proposed prior art reference combination.

Remarks Directed to the Rejection of Claims 11, 12, 15, and 16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski in View of Keener and Gebeyehu in Further View of Kitadai:

Applicant incorporates in its entity the above remarks regarding Niedzinski in view of Keener and Gebeyehu in that, alone or in combination, they are deficient in rendering obvious the claimed invention.

The teaching of Kitadai fails to correct the above shortcoming as this reference is limited to teaching DNA encapsulated in LIPOFECTIN reagent. There is no suggestion in Niedzinski, Keener, Gebeyehu or Kitadai to substitute C(3)-functionalized cholates for the LIPOFECTIN of Kitadai. Indeed, all biological protective and delivery functionality in Niedzinski is taught in the presence of the transfection agent DOTAP, DOPE, or DMDHP. These results are summarized as "the addition of the cholate lipids does not appear to compromise the gastroprotection afforded by lipoplex formulation of DNA." (Niedzinski, pg. 725.) Further, Niedzinski teaches nucleic acid delivery to target cells using DOPE and DMDHP encapsulating molecules where "DMDHP was selected for the transfection experiments based on the superior transfection activity exhibited by DMDHP." (Niedzinski, pg. 725.) All results in Niedzinski are to stimulate or inhibit the transfection activity of DMDHP. Niedzinski concludes that "cholate 5 may be suitable for addition to a therapeutic lipoplex preparation." Id. (emphasis added) Thus, a person having ordinary skill in the art recognizes that Niedzinski teaches addition to, not substitution for transfection agents disclosed therein or those of Kitadai. As such, Kitadai fails to correct the shortcomings of Niedzinski in view of Keener and Gebeyehu.

Summary

It is submitted that no prima facie case of obviousness is established for any claim and it is respectfully submitted that the rejections under 35 U.S.C. 103(a) are improper and that the finality of the rejections is likewise improper. Applicant, therefore, respectfully requests withdrawal of the rejections, withdrawal of the finality of the rejections, and allowance of the pending claims.

Review of all the outstanding bases for rejection is hereby requested.

Respectfully submitted,
/Avery N. Goldstein, Ph.D./
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